REMARKS

The Final Office Action of September 29, 2003, and the Advisory Action of January 14, 2004, have been received and reviewed. Claims 1-11, 14-16, 18, and 21-25 are pending in the application and all pending claims stand rejected. Applicants propose to amend claims 11, 15, 24 and 25 as set forth herein. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Information Disclosure Statement

The Advisory Action noted that the "Information Disclosure Statement submitted on December 4, 2003 has not been considered by the Examiner because certification, petition, and a petition fee are required in order for the Information Disclosure Statement, which is submitted after final Action, to be considered." (Advisory Action of January 14, 2003, page 2).

Applicants respectfully submit that the Examiner consider the Information Disclosure Statement filed on December 4, 2003, because the applicants have complied with 37 C.F.R. § 1.97. 37 C.F.R. § 1.97(d) states "An information disclosure statement **shall be considered** by the Office if filed by the applicant after the period specified in paragraph (c) [*i.e.*, after final] of this section, provided that the information disclosure statement is filed on or before payment of the issue fee and is accompanied by: (1) The statement specified in paragraph (e) of this section; and (2) The fee set forth in § 1.17(p)." (37 C.F.R. § 1.97(d) (emphasis added). Thus, since the applicants complied with 37 C.F.R. § 1.97(d), the information disclosure statement **shall be considered** by the Office.

The Information Disclosure Statement submitted on December 4, 2003, did include the statement required by 37 C.F.R. § 1.97(e) and the fee of $180.00 set forth in § 1.17(p). Thus, consideration of the references submitted in the Information Disclosure Statement submitted on December 4, 2003 is requested.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 11, 15-18, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite. Applicants respectfully traverse the rejections as set forth herein.

It was noted that the language of claim 11 reciting "a method of screening a compound that inhibits the binding of a ligand with the signaling pathway of the cytoplasmic part of a chimeric receptor" was thought to be unclear as to the metes and bounds of the claim. (Final Office Action, page 3). Although applicants do not agree that claim 11 is indefinite, in order to expedite prosecution, applicants propose to amend claim 11 to read on "a method of screening for a compound that inhibits the binding of a ligand with the extracellular part of a chimeric receptor and/or **inhibits** the signaling pathway of the cytoplasmic part of a chimeric receptor" in order to clarify claim 11. As proposed to be amended, the metes and bounds of claim 11 should be clear.

The Advisory Action indicated that claims 11, 15, 16, 18, 24 and 25 do not recite "contacting the eukaryotic cells with a ligand of the chimeric receptor." (Advisory Action, page 1). Although applicants do not agree that any of the claims are indefinite, to expedite prosecution, applicants propose to amend each of claims 11, 15, 24 and 25 to include an element directed towards contacting the eukaryotic cell with the ligand in accordance with the Examiner's suggestions. Support for the proposed amendments is found, *inter alia*, at paragraphs **[0015]-[0017]**, **[0019]**, **[0103]**, and **[0112]** of the as-filed specification.

Indefinite rejections of record were also maintained since it was thought "the claims are indefinite because the steps recited by the methods do not necessarily achieve the goal set forth in the preamble." (Final Office Action at page 2). The Final Office Action stated "the method steps never require measuring and/or comparing the binding of a ligand to a chimeric receptor in the presence or absence of a test compound" (*Id.* at page 3) and the Advisory Action indicated "activation or deactivation of the reporter system is not an indicator of whether a compound (an antagonist) binds to a chimeric receptor." (Advisory Action at page 2). However, measuring, comparing, or testing of test compounds is not required to screen for a compound.

As stated in the MPEP, "the test for definiteness under 35 U.S.C. 112, second paragraph, is whether 'those skilled in the art would understand what is claimed when the claim is read in light of the specification.'" (M.P.E.P. § 2173.02, *citing Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). Each of independent method claims 11, 15, 24 and 25 includes an element that achieves the goal of

screening. For instance, claim 11 recites in part "selecting cells in which the cell's reporter system is **inactivated**," claim 15 recites in part "selecting cells in which the cell's reporter system is **activated**," claim 24 recites in part "assaying the inhibiting activity of the ligand-receptor binding of each element of said series of compounds by assaying the **deactivation** of the reporter system," and claim 25 recites in part "assaying the inhibiting activity of the ligand-receptor binding by assaying the **activation** of the reporter system." The as-filed specification indicates that "'reporter system' means every compound of which the synthesis and/or modification and/or complex formation can be detected and/or be used in a screening and/or selection system." (Specification, as-filed, paragraph **[0041]**). Thus, when the pending claims are read in light of the specification, one of ordinary skill in the art would understand that the screening methods of independent claims 11, 15, 24 and 25 are accomplished by ascertaining whether a reporter system is activated or inactivated.

Further, the claims are not directed to methods of **comparing or measuring** binding to a test compound, but, rather, are directed to methods of **screening**. Thus, all that is required is that the steps of claims 11, 15, 24 and 25 accomplish methods of screening. The use of a blank or test compound is not **required** to accomplish the screening as asserted by the Final Office Action. (*See*, Final Office Action at page 3). The activation or deactivation of the reporter system is all that is required to perform the screening methods.

The applicants cited U.S. Pat. 5,283,173 in the Amendment filed July 23, 2003, as support to indicate that it is known in the art that screening systems may give false positives or negatives and that a comparison to a test compound is not needed. In response to the applicants' argument, the Final Office Action indicated "it is well settled that the prosecution of one patent application does not affect the prosecution of an unrelated application." (Final Office Action at page 4). However, as stated in the MPEP, an "applicant may submit factual affidavits under 37 CFR 1.132 or **cite references** to show what one skilled in the art knew at the time of filing the application." (M.P.E.P. § 2164.05) (*Emphasis added*).

Since the test for definiteness under 35 U.S.C. § 112, second paragraph, is whether one skilled in the art would understand what is being claimed when the claim is read in light of the specification, the applicants may cite patent references to show what those skilled in the art knew

or would understand. (*See*, M.P.E.P. § 2173.02, *supra*). Thus, as stated by one of ordinary skill in the art "[i]f the bait and prey proteins are able to interact, they bring into close proximity the two domains of the transcriptional activator. This proximity is sufficient to cause transcription, which can be **detected by the activity of a reporter gene** that contains a binding site for the DNA-binding domain." (U.S. Pat. 6,332,897, col. 1, lines 49-54) (Emphasis added). As stated in another patent directed to methods of screening, "measuring interaction of the first and second proteins of interest via selective activation of the first, second and third reporter genes." (U.S. Pat. 6,326,150, col. 4, lines 42-44). The references do not mention a requirement or need for a test compound.

Although applicants do not agree that any of the claims are indefinite, to expedite prosecution, applicants propose to amend claims 24 and 25 to read on comparing the inhibiting activity of said series of compound to a control compound in accordance with the suggestions of the Examiner. Support for the proposed amendments is found in the as-filed specification at paragraphs **[0105]**, **[0107]**, **[0109]**, and **[0112]**. Thus, claims 24 and 25 should be definite.

Reconsideration and withdrawal of the indefiniteness rejections of claims 11, 15-18, 24 and 25 are requested.

Rejections under 35 U.S.C. § 103

Claims 1-6, 10, 11, 14-16, 18 and 21-25 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Pestka et al. in view of Trueheart et al. Applicants respectfully traverse the rejections as set forth herein.

A *prima facie* case of obviousness cannot be established with regard to any of independent claims 1, 15, 24 or 25 since no suggestion or motivation exists to combine the cited references. In formulating the obviousness rejections, the Office is using an impermissible hindsight reconstruction of the applicants' invention as a suggestion or motivation to combine Trueheart et al. with Pestka et al.

As stated by the Federal Circuit "defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." (*Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 880, 45 U.S.Q.P.2d 1977, 1981 (Fed. Cir.

1998)). Thus, when the Final Office Action states that "it is the benefit of the methods taught by Pestka et al. and Trueheart that motivates one skilled in the art to combine the teaching of Pestka et al. with the teaching of Trueheart et al.," the Final Office Action is using the solutions of Pestka et al. and Trueheart et al. as the motivation to combine the references which results in a hindsight reconstruction of the applicants' invention. (Final Office Action, page 5).

In order to guard against an improper hindsight combination of references, the Federal Circuit indicated a "factual question of motivation is material to patentability, and could not be resolved on subjective belief and unknown authority. It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to '[use] that which the inventor taught against its teacher.'" (*In re Lee*, 277 F.3d 1338, 1344, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002), *citing W.L. Gore v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983)).

Thus, the statement in the Final Office Action that

"it would have been obvious to one having ordinary skill in the art at the time the invention was made, as a matter of choice, instead of exogenous addition of a test compound to cells, to use a second gene encoding a compound taught by Trueheart et al. so that a compound can be expressed, an autocrine or anti-autocrine loop can be created in cells taught be Pestka et al., and such cells can be used for the screening method taught be Pestka et al. with a reasonable expectation of success. One would have been motivated to do so because endogenous expression of polypeptides in a cDNA library allows rapid screening of large numbers of polypeptides as taught and by Trueheart et al."

is a subjective, conclusory statement because it is based on unknown authority. (Final Office Action at page 5) (Emphasis added). When the Patent Office "rel[ies] on what they assert to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record," which the Patent Office has not done here. (*In re Lee*, *supra*, at 1345).

The Advisory Action stated "[i]t is further noted that Applicants acknowledge in the specification (top of page 8) that an antagonist screening system can be realized by using the autocrine loop and adding possible inhibitors to the medium, but it is clear to people skilled in the art that, alternatively, the cell can be transformed with genes encoding candidate inhibitors,' supporting the obviousness rejection set forth in the record." (Advisory Action at page 2).

It is noted that the passage cited in the Advisory Action is taken from the SUMMARY OF THE INVENTION section of the applicants' specification and that the first part of the quoted paragraph was omitted. The first part of paragraph **[0018]** recites "A further aspect of the invention is the screening of compounds that are antagonists of the ligand-receptor binding. Due to the fact that these compounds can be screened for the toxicity of *gpt* expression in D-MEM + 6-TG medium, it is possible to set up an antagonistic screening system for compounds that inhibit and/or compete with the binding of the ligand to the chimeric receptor. This can be realized by ..." Thus, the Advisory Action is relying on the applicants' disclosure to formulate the obviousness rejection.

The MPEP indicates that a judgment on obviousness may "tak[e] into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and **does not include knowledge gleaned only from applicant's disclosure**." (M.P.E.P. § 2145, *quoting In re McLaughlin*, 443 F.2d 1392, 1395, 170 UQPQ 209, 212 (CCPA) (emphasis added)). As further stated by the Federal Circuit "[o]bviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." (*Para-Ordnance Mfr. Inc., v. SGS Importers Intl., Inc.*, 73 F.3d 1085, 1087, 37 U.S.P.Q.2d 1237, 1239 (Fed. Cir. 1995)). Thus, since the Advisory Action is citing a teaching or suggestion from the inventors' SUMMARY OF THE INVENTION, obviousness cannot be established.

As a further indicia of non-obviousness, one of ordinary skill in the art would not expect a gene encoding a test compound to function in the same manner as a test compound exogenously added to a cell as a matter of choice. For instance, the gene would have to actually express the test compound in a manner that it could be screened, in contrast to contacting a cell with an already produced, exogenous test compound. Further, if a cell expresses the gene encoding the test compound, the test compound will be present in the interior of the cell which is in contrast to exogenously adding the test compound to the exterior of the cell. In either instance, the test compound will have to be transported across the cell membrane. Thus, how the test compound is transported across the cell membrane or how the test compound interacts with the compound that is screened cannot simply be a matter of choice.

One reason it is not simply a matter of choice is that one skilled in the art would not expect the autocrinic loops including the G-protein coupled receptors (GPCRs) of Trueheart et al. to function in the cells of Pestka et al. in the same manner as a test compound exogenously added to a cell since the cells of Pestka et al. include several hundreds of GPCRs. "One factor which can complicate the use of heterologous expression systems for ligand fishing involves the presence of endogenous receptors in mammalian cell lines and in particular, clonal variation in the pattern of endogenous receptor expression in cells derived from the same parental cell line." (Wilson et al., *Orphan G-protein-coupled receptors: the next generation of drug targets?, British Journal of Pharmacology*, vol. 125, 1387-1392, at p. 1389 (1998) (previously submitted)). Further, "the ability to genetically delete endogenous GPCRs from yeast to generate a 'null' background is one of the major advantages in using yeast model systems for orphan receptor screening." (*Id.* at 1390).

Trueheart et al. recognized this problem by reciting "it will be understood to achieve selection or screening, the host cell must have an appropriate phenotype. For example, generating a pheromone-responsive chimeric HIS3 gene in a yeast that has a wild-type HIS3 gene would frustrate genetic selection." (Trueheart et al., page 20). Thus, Trueheart et al. recognized that the wild-type gene would frustrate genetic selection because of the background produced by the wild-type gene and, thus, teaches away from combining the teachings of Trueheart et al. with Pestka et al.

Further, the cells of Pestka et al. would be expected to produce a background that may make screening the mammalian cells nearly impossible. As known in the art, mammalian cells include several hundred GPCRs, while only two GPCRs have been identified in yeast cells. (*See, e.g.*, Versele et al., *Sex and sugar in yeast: two distinct GPCR systems*, EMBO reports, vol. 2, no. 7, 574-579 (2001) (previously submitted). Thus, the background expected from the presence of a gene encoding a test compound in mammalian cells of Pestka et al. would frustrate selection.

A *prima facie* case of obviousness also cannot be established since one of ordinary skill in the art would not have a reasonable expectation of success in combining Pestka et al. with Trueheart et al. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but

whether the claimed invention as a whole would have been obvious." (M.P.E.P. § 2141.02, *citing Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983) and *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983) (*emphasis in original*)).

One skilled in the art would not reasonably expect the chimeric receptor of Pestka et al. to function in the yeast cells of Trueheart et al. Since the receptors of Trueheart et al. are functionally integrated in the signaling pathway, *e.g.*, the endogenous signaling pathway (*See*, Trueheart et al., page 16, line 26 through page 17, line 1) of the yeast cells of Trueheart et al., the chimeric receptor of Pestka et al. would not be expected to work in the yeast cells of Trueheart et al. without undue experimentation or testing. Thus, the unsupported, conclusory statement in the Final Office Action, by itself, that "as a matter of choice, instead of exogenous addition of a test compound to cells, to use a second gene encoding a compound," without an objective teaching cannot provide the suggestion or motivation to combine the teachings of the cited references. (Final Office Action at page 5).

Since the Final Office Action is using an unsupported, conclusory statement as a suggestion or motivation to combine Trueheart et al. with Pestka et al., and the applicants have provided references evidencing why one of ordinary skill in the art would not expect the disclosures of Pestka et al. and Trueheart et al. to work as suggested by the Final Office Action, a *prima facie* case of obviousness cannot be established with regard to any of independent claims 1, 15, 24 or 25.

Accordingly, reconsideration and withdrawal of the obviousness rejections of claims 1-6, 10, 14-16, 18 and 21-25 are requested.

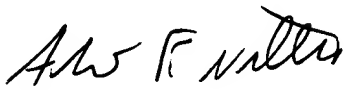
ENTRY OF AMENDMENTS

The proposed amendments to claims 11, 15, 24 and 25 should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings, do not add any new matter to the application and should place the application in condition for allowance. The amendment to claim 11 should also not raise new issues or require a further search since the amendment complies with requirements as to form. The addition of the element directed to contacting the eukaryotic cell with the ligand to claims 11, 15, 24 and 25 should be entered since it complies with requirements of form and adopts suggestions of the Examiner. Further, the addition of the element directed to comparing the inhibiting activity of the series of compounds to a control compound in claims 24 and 25 should be entered since they adopt suggestions of the Examiner. Finally, if the Examiner determines that the amendment does not place the application in condition for allowance, entry is respectfully requested since it certainly removes issues for appeal.

CONCLUSION

In view of the amendments and remarks presented herein, applicants respectfully submit that the claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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